(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 112 758**
**B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **20.08.86**

(51) Int. Cl.[4]: **C 07 J 31/00,** A 61 K 31/565

(21) Application number: **83402376.4**

(22) Date of filing: **08.12.83**

(54) **16-Ketoandrostene-17-dithioketals.**

(30) Priority: **27.12.82 US 453314**

(43) Date of publication of application:
**04.07.84 Bulletin 84/27**

(45) Publication of the grant of the patent:
**20.08.86 Bulletin 86/34**

(84) Designated Contracting States:
**AT BE CH DE FR GB IT LI LU NL SE**

(56) References cited:
**US-A-4 252 733**
**US-A-4 361 559**

(73) Proprietor: **E.R. Squibb & Sons, Inc.**
**Lawrenceville-Princeton Road**
**Princeton, N.J. 08540 (US)**

(72) Inventor: **Varma, Ravi K.**
**293 Deer Run Drive**
**Belle Mead New Jersey (US)**

(74) Representative: **Maiffret, Bernard et al**
**Law Offices of William J. Rezac 49, avenue**
**Franklin D. Roosevelt**
**F-75008 Paris (FR)**

**EP 0 112 758 B1**

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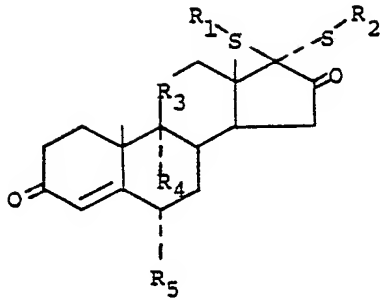
Courier Press, Leamington Spa, England.

**Description**

Steroids having the formula



I

and the 1,2-dehydro and 6,7-dehydro derivatives thereof, have topical aintiinflammatory activity. In formula I, and throughout the specification, the symbols are as defined below.

$R_1$ and $R_2$ are the same of different and each is alkyl, cycloalkl or aryl;

$R_3$ is cabonyl, β-hydroxymethylene or β-acetyloxymethylene;

$R_4$ is hydrogen or halogen; and

$R_5$ is hydrogen, methyl, hydroxy, alkanoyl, alkanoyloxy, or halogen.

The term "aryl", as used throughout the specification either individually or as part of a larger group, refers to phenyl of phenyl substituted with one or two alkyl, alkoxy or halogen groups.

The term "halogen", as used throughout the specification either individually or as part of a larger group, refers to fluorine, chlorine, bromine and iodine.

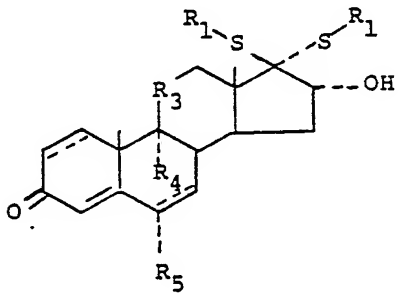
The terms "alkyl" and "alkoxy", as used throughout the specification either individually or as part of a larger group, refer to groups having 1 to 12 carbon atoms.

The steroids of formula I, and the 1,2-dehydro and 6,7-dehydro derivatives thereof, are topical antiinflammatory agents that can be used to treat skin conditions such as dermatitis, psoriasis, sunburn, eczema neurodermatitis, or anogenital pruritus, and in inhalation therapy for tropical treatment of allergy and asthma.

For the treatment of skin conditions, the tropical antiinflammatory steroids of this invention may be administered in a conventional pharmaceutical carrier in the form of a cream, ointment or lotion. The steroids will preferably be used in the range of 0.01 to 5.0% by weight of the vehicle, preferably 0.05 to 2.0% by weight of the vehicle.

For the topical treatment of allergy and asthma the tropical antiinflammatory steroids of this invention may be administered in the conventional manner, *e.g.,* as solid medicament which has been atomized. United States patents 3,948,264 and 4,147,166 are exemplary of the literature which describes divices that can be used to administer solid medicaments for inhalation therapy.

The steroids of formula I, and the 1,2-dehydro and 6,7-dehydro derivatives thereof, wherein $R_1$ and $R_2$ are the same, can be prepared by oxidizing the corresponding 16α-hydroxyandrostene having the formula

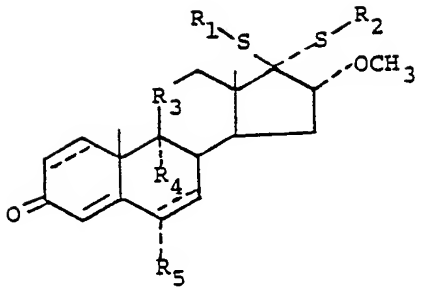


II

The oxidation is preferably accomplished using a mixture of dimethylsulfoxide and acetic anhydride.

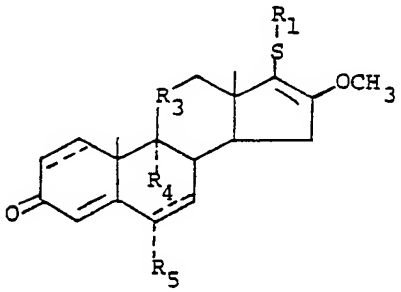
The steroid of formula I, and the 1,2-dehydro and 6,7-dehydro derivatives thereof, wherin $R_1$ and $R_2$ are different, can be prepared by first heating a 16α-methoxyl-17-symmetrical dithioketal androstene having the formula

III



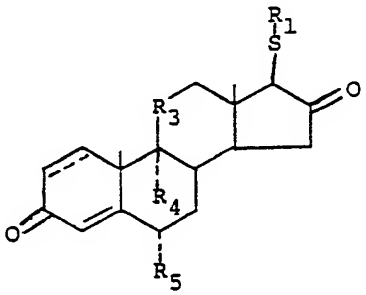
to yield the corresponding (unstable) androstene having the formula

IV



The androstene of formula IV is hydrolyzed directly *(i.e.,* the steroid of formula IV is not isolated) with dilute mineral acid to yield the corresponding androstene having the formula

V



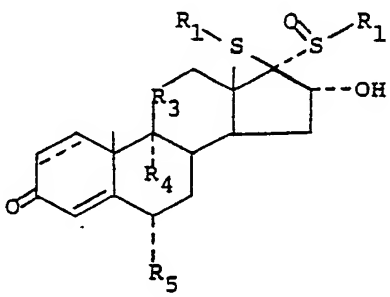
Conversion of an androstene of formula V to the desired product of formula I can be accomplished by reaction with the appropriate compound having the formula

$$R_2\text{-}S\text{-}SO_2\text{-}R_2 \qquad IV$$

The reaction will preferably be run in an organic solvent such as tetrahydrofuran in the presence of a base such as n-butyl lithium and a secondary amine such as diisopropylamine.

Alternatively, the steroids of formula I, and the 1,2-dehydro and 6,7-dehydro derivatives thereof, wherein $R_1$ and $R_2$ are different, can be prepared by first oxidizing an androstene of formula II with a peracid e.g., m-chloroperbenzoic acid), preferably in an organic solvent, to yield the corresponding androstene having the formula

VII



Reaction of an androstene of formula VII with dimethylsulfoxide and acetic anhydride yields the corresponding androstene of formula V. Conversion of an androstene of formula V to a product of formula I can be accomplished using the procedure described above.

In the above-described reaction it may be necessary (when, in the desired product, $R_3$ is β-hydroxymethylene) to protect the 11β-hydroxyl group of the steroid starting materials and intermediates. An exemplary family of protecting groups is the acyl family, *e.g.,* alkanoyl groups such as acetyl. Means for protection and deprotection of the 11β-hydroxyl group are well known in the art.

The preparation of steroids of formulas II and III is disclosed in United States patent 4,361,559 issued November 30, 1982.

The compounds of formula VI can be prepared using art-recognized techniques; see for example, D. J. Smith et al., *Biochemistry, 14,* 776 (1975).

The following examples are specific embodiments of this invention.

Example 1

9-Fluoro-11β-hydroxy-17,17-bis(methylthio) androsta-1,4-diene-3,16-dione

A) 11β-(Acetyloxy)-9-fluoro-17-(methylsulfonyl)-androsta-1,4,16-trien-3-one

To a solution of 20 g (51.34 mmlole) of 11β-(acetyloxy)-17-(methylthio)-9-(fluoro)-androsta-1,4,16-trien-3-one in dichloromethane (350 ml) was added 22.8 g (113 mmole) of *m*-chloroperoxybenzoic acid (85.6%) in 350 ml of dry dichloromethane and the solution was stirred in room temperature under nitrogen for 40 minutes. It was then washed with a saturated sodium bicarbonate solution and water, dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* to give 21.4 g of the title compound, melting point 273—275°C, *dec.*

B) 11β-(Acetyloxy)-9-fluoro-16α-hydroxy-androsta-1,4-diene-3,17-dione

A solution of 21 g of 11β-(acetyloxy)-9-fluoro-17-(methylsulfonyl)androsta-1,4,16-trien-3-one and 65 ml of formic acid (10%, $^v/_v$ in 1.7 liters of acetone (reagent grade) was cooled to −10°C (salt-ice bath). A solution of 19 g of potassium permanganate in 650 ml of acetone (reagent grade) was added at −10°C over the course of 20 minutes. The mixture was stirred at approximately −10°C for 45 minutes, quenched with a solution of 5% sodium bisulfite (300 ml) and acetone (300 ml), and gradually warmed up to room temperature. Hyflo was added and the mixture was filtered through a bed of Hyflo. The filtrate was evaporated in vacuo to give a slurry. This was extracted with chloroform, and the chloroform solution was washed with water, dried over anhydrous $Na_2SO_4$ and evaported in vacuo to give a foam. This was dissolved in chloroform-hexane (7:3) and chromatographed on a 100 g-silica gel column, eluting successively with chloroform-hexane (7:3 and 9:1) chloroform, chloroform-ethyl acetate (4:1) and chloroform-methanol (9:1) to give 9.5 g of the title compound, melting point 241—243°C, and 4.0 g of its 16β-hydroxy isomer, melting point 229—231°C, *dec.*

C) 11β-(Acetyloxy)-9-fluoro-16α-hydroxy-17,17-bis(methylthio)androsta-1,4-dien-3-one

A solution of 9.5 g (25.2 mmole) of 11β-(acetyloxy)-9-fluoro-16α-hydroxyandrosta-1,4-diene-3,17-dione in glacial acetic acid (100 ml) and dry dichloromethane (50 ml) was cooled in an ice bath. A solution of methyl mercaptan in dry dichloromethane (2M, 100 ml), and then, boron trifluoride etherate (8 ml) were added. The solution was stirred at 0°C under nitrogen for 45 minutes, poured into cold water and extracted with chloroform. The chloroform solution was washed with a saturated sodium bicarbonate solution and water, dried over anhydrous $Na_2SO_4$ and evaported *in vacuo* to give a foam (13 g). This was mixed with acetone (400 ml), water (25 ml) and iodomethane (13 ml) and refluxed for 75 minutes. The solvent was evaporated *in vacuo* at 30—35°C to give a slurry; heating above 30—35°C was avoided. The slurry was diluted with chloroform, washed with a 10% sodium thiosulfate solution and water, dried over anhydrous $Na_2SO_4$ and evaporated in vacuo to give a foam. This was dissolved in chloroform-hexane (3:2) and chromatographed on a 100 g-silica gel column, eluting successively with chloroform-hexane (3:2 and 7:3), chloroform and chloroform-ethyl acetate (9:1) to give 6.3 g of a slightly impure title compound. Crystallization from ethyl acetate-hexane gave 6.0 g of material, melting point 218—220°C.

D) 11β-(Acetyloxy)-9-fluoro-17,17-bis(methylthio)-androsta-1,4-diene-3-16-dione

A solution of 3.0 g (6.6 mmole) of 11β-(acetyloxy)-9-flouro-16α-hydroxy-17,17-bis(methylthio)-androsta-1,4-dien-3-one in solution of dry dimethylsulfoxide (30 ml), acetic anhydride (20 ml) and glacial acetic acid (10 ml) was stirred at room temperature under nitrogen overnight. The resulting solution was poured into cold water and extracted with dichloromethane. The dichloromethane solution was washed with saturated sodium bicarbonate solution and water, dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* to give 2.9 g of solid, melting point 225—227°C.

E) 9-Flouro-11β-hydroxy-17,17-bis(methylthio)-androsta-1,4-diene-3,16-dione

To a stirred solution of 1.7 g (3.76 mmole) of 11β-(acetyloxy)-9-fluoro-17,17-bis(methylthio)-androsta)-1,4-diene-3-16-dione in a mixture of methanol (70 ml), tetrahydrofuran (50 ml) and water (5 ml) was added 10% potassium carbonate solution dropwise until the pH of solution was about 10. The solution was

allowed to stir at room temperature under nitrogen for 2 hours and quenched with a slight excess of concentrated acetic acid. The solvent was evaporated *in vacuo* to give a slurry. This was diluted with water and extracted with dichloromethane. The dichloromethane solution was dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* to give 1.35 g of the title compound. Recrystallization of this from acetone-hexane gave 70 mg of an analytical specimen, melting point 293—294°C, dec.

Anal. Calc'd for $C_{12}H_{27}FO_3S_2$: C, 61.43: H, 6.63: F, 4.63: S, 15.62
Found: C, 61.42; H, 6.43; F, 4.60; S, 15.79

Example 2

17α-(Ethylthio)-9-fluoro-11β-hydroxyl-17-(methylthio)-androsta-1,4-diene-3,16-dione

A) 11β-(Acetyloxy)-9-fluoro-16α-hydoxy-17α-methylsulfinyl-17-(methylthio)androsta-1,4-diene-3-one

To a cold solution of 2.5 g (5.62 mmole) of 11β-(acetyloxy)-9-fluoro-16α-hydroxy-17,17-bis-(methylthio)androsta-1,4-dien-3-one (see example 1C) in a mixture of dichloromethane (100 ml) and methanol (20 ml) at −78°C (acetone-Dry ice bath) was added a solution of 1.4 g (5.62 mmole) of *m*-chloroperoxybenzoic acid (85%) in dichloromethane (20 ml) over the course of 3 minutes. The resulting solution was gradually warmed to 0°C over the course of 1.5 hours, poured into cold water and extracted with dichloromethane. The dichloromethane solution was washed with saturated $NaHCO_3$ solution and water, dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* at 30°C to give 2.54 g of the title compound. (This compound is not very stable on standing and must be used as soon as it is prepared).

B) 11β-(Acetyloxy)-9-fluoro-17-(methylthio)androsta-1,4-diene-3,16-dione

A solution of 11β-(acetyloxy)-9-fluoro-16α-hydroxy-17α-(methylsulfinyl)-17-(methylthio)androsta-1,4-diene-3-one (50 g) in a mixture of dry dimethylsulfoxide (3.0 ml), acetic anhydride (2 ml) and acetic acid (1 ml) was stirred at room temperature for 4.0 hours. The mixture was then poured into cold water and extracted with dichloromethane. The extracts were combined, washed with water, dried (anhydrous $MgSO_4$), and evaporated. The residue was crystallized from ethyl actetate-hexane to afford the title compound (36 mg), melting point 235—237°C.

C) Ethyl ethanethiosulfonate

Ethyl disulfide (36.68 g, 0.3 mole) was dissolved in 90 ml of glacial acetic acid in a 500 ml three neck flask fitted with a reflux condenser and a 100 ml-dropping funnel. The reaction flask was first cooled to 0°C with vigorous stirring. A solution of 68.1 g of hydrogen peroxide (30%) was added slowly through the dropping funnel while maintaining the temperature below 10°C. Initially the reaction mixture existed as two layers. After addition of hydrogen peroxide, the solution was stirred for 30 minutes at 0°C and the flask was then slowly warmed to 60°C for about 1.0 hours. The reaction mixture gradually became a homogeneous solution. (Warming the flask slowly is essential to prevent the reaction from becoming extremely exothermic.) After tests for peroxide became negative (KI-starch paper), the glacial acetic acid was removed *in vacuo* at 40°C. The oil was diluted with 150 ml of saturated $NaHCO_3$ and extracted thoroughly with chloroform. The chloroform solution was dried over anhydrous $Na_2SO_4$ and evaported in vacuo to give an oil. Distillation under 1.5 mm of Hg gave 37.5 g of the title compound, boiling point 90—96°C.

D) 11β-(Acetyloxy)-17α-(ethylthio)-9-fluoro-17-(methylthio)androsta-1,4-diene-3-16-dione

To a solution of 76 mg (0.75 mmole) of diisopropylamine in 2 ml of dry tetrahydrofuran at −78°C (acetone-Dry ice bath) was added dropwise 0.44 ml of *n*-butyl lithium (1.7 M in hexane) under nitrogen. After stirring 40 minutes at −78°C, a solution of 203 mg (0.5 mmole) of 11β-(acetyloxy)-9-fluoro-17β-(methylthio)androsta-1,4-diene-3,16-dione in 2 ml of dry tetrahydrofuran was added dropwise. The mixture was gradually warmed to 0°C over the course of 1.0 hour. This was slowly added to a solution of 771 mg (5 mmole) of ethyl ethanethiosulfonate in 2 ml of dry tetrahydrofuran at 0°C under nitrogen. After stirring for 30 minutes, the resulting solution was poured into water and extracted with chloroform. The chloroform solution was dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* to give an oil. This was dissolved in chloroform and chormatographed on 2 precoated silica gel TLC plates (E. Merck, 20 cm × 0.5 mm, 1:4 ethyl acetate-chloroform for development) to give 46 mg of the title compound.

A second run using 406.5 mg (1 mmole) of 11β-(acetyloxy)-9-fluoro-17β-(methylthio)androsta-1,4-diene-3,16-dione gave an additonal 114 mg of the title compound.

E) 17α-(Ethylthio)-9-fluoro-11β-hydroxy-17-(methylthio)androsta-1,4-diene-3,16-dione

A solution of 160 mg (0.343 mmole) of 11β - (acetyloxy) - 17α - (ethylthio) - 9 - fluoro - 17 - (methylthio)androsta-1,4-diene-3,16-dione in a mixture of methanol (10 ml) tetrahydrofuran (5 ml) and water (0.1 ml) was stirred with 0.7 ml of a 3N sodium hydroxide solution at room temperature under nitrogen for 1.0 hour. The resulting solution was quenched with a slight excess of concentrated acetic acid. The solvent was evaporated *in vacuo* to give a slurry, which was diluted with water and extracted with

chloroform. The chloroform solution was dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* to give a foam (135 mg). This was dissolved in chloroform-hexane (7:3) and chromatographed on a 15 g-silica gel column, eluting with chloroform-hexane (7:3) to give 115 mg of the title compound. Crystallization from acetone-hexane gave 90 mg of analytical specimen, melting point 262—264°C, *dec.*

Example 3

17,17-bis-(Ethylthio)-9-fluoro-11β-hydroxyandrosta-1,4-diene-3,16-dione

A) 11β-(Acetyloxy)-17,17-bis(ethylthio)-9-fluoro-16α-hydroxyandrosta-1,4-diene-3-one

To a solution of 11β(acetyloxy)-9-fluoro-16α-hydroxyandrosta-1,4-dien-3,17-dione (1.0 g; see example 1B) in glacial acetic acid (30 ml) containing ethanethiol (1.0 ml), undistilled boron trifluoride etherate (1.2 ml) was added. After 1.0 hour, an additional 1.0 ml each of ethanethiol and boron trifluoride etherate were added, and three minutes later, the solution was added to water and extracted with chloroform. The chloroform solution was washed with water, a dilute $NaNCO_3$ solution and water, dried ($MgSO_4$) and evaporated to afford the crude product as a gum. This was subjected to preparative thin layer chromatography on four Analtech 2X200X200 mm silica gel plates using chloroform-ethyl acetate (9:1) for developments and chloroform-methanol (4:1) for extraction of the bands to isolate, in the order of increasing polarity, 11β,16α-di(acetyloxy)-17,17-bis(ethylthio)-9-fluoroandrosta -1,4-diene-3,17-dione (147 mg), the title compound (314 mg, after one crystallization from ethyl acetate-hexane, melting point was 181—182°C), an uncharacterized compound (40 mg) and the starting steroid (430 mg).

B) 11β-(Acetyloxy)-17,17-bis(ethylthio)-9-fluoroandrosta-1,4-diene-3,16-dione

A solution of 11β-(acetyloxy)-17,17-bis(ethylthio)-9-fluoro-16α-hydroxyandrosta-1,4-diene-3-one (100 mg, 0.207 mmole) in a mixture of dry dimethylsulfoxide (2.0 ml), acetic anhydride (0.7 ml) and acetic acid (0.1 ml) was left standing at room temperature for 18 hours. The mixture was then added to water and was extracted with chloroform. The chloroform solution was washed with water, dried ($MgSO_4$) and evaporated to afford the title compound (94 mg) as a solid.

C) 17,17-bis(Ethylthio)-9-fluoro-11β-hydroxyandrosta-1,4-diene-3,16-dione

11β-(Acetyloxy)-17,17-bis(ethylthio)-9-fluoroandrosta-1,4-diene-3,16-dione was dissolved in a mixture of methanol (3.0 ml) and tetrahydrofuran (3.0 ml) and was exposed to 3M sodium hydroxide (0.3 ml) for 1.0 hour under an atmosphere of nitrogen. The mixture was then added to water and was extracted with chloroform. The chloroform solution was washed with water, dried ($MgSO_4$) and was evaporated to afford the title compound as a solid (80 mg). One crystallization of this from ethyl acetate-hexane followed by drying gave the analytical specimen of the title compound (58 mg), melting point 268—270°C (*dec.*, discoloration starts from *ca* 200°C.

Example 4

9-Fluoro-11β-hydroxy-17β-(methylthio)-17-(propylthio)-androsta-1,4-diene-3,16-dione

A) *n*-Propyl *n*-propanethiosulfonate

*n*-Propyl disulfide (37.575 g, 0.25 mole) was dissolved in 90 ml of glacial acetic acid in a 500 ml three-neck flask fitted with a reflux condenser and 100 ml dropping funnel. The reaction flask was first cooled to 0°C, and with vigorous stirring, a solution of 56.7 g (0.5 mole) of hydrogen peroxide (30%) was added slowly through the dropping funnel while maintaining the temperature below 10°C. Initially the reaction mixture existed as two layers. After addition of hydrogen peroxide, the solution was stirred for 30 minutes at 0°C and the flask was then slowly warmed to 60°C over the course of one hour, while it gradually became a homogeneous solution. [Slow warming of the flask was necessary; otherwise the reaction becomes extremely exothermic.] After a test for peroxide became negative (KI-starch paper), the glacial acetic acid was removed *in vacuo* at 45°C. The oil was diluted with 150 ml of saturated $NAHCO_3$ solution and extracted throughly with chloroform. The chloroform solution was dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* to give an oil. Distillation under 2.0 mm of Hg gave 29.1 g of the title compound, boiling point 110—115°C.

B) 11β-(Acetyloxy)-9-fluoro-17β-(methylthio)-17-(propylthio)androsta-1,4-diene-3,16-dione

To a solution of 76 mg (0.75 mmole) of diisopropylamine in 2 ml of dry tetrahydrofuran at −78°C (acetone-Dry ice bath) was added dropwise 0.44 ml of *n*-butyllithium (1.7 M in hexane) under nitrogen. After stirring 10 minutes at −78°C, a solution of 203 g (0.5 mmole) of 11β-(acetyloxy)-9-fluoro-17β-(methylthio)-androsta-1,4-diene-3,16-dione (see example 2B) in 2.5 ml of dry tetrahydrofuran was added dropwise. The mixture was gradually warmed to 0°C over the course of 1.5 hours. This was slowly added to a solution of 791.5 mg (5 mmole) of *n*-propyl *n*-propanethiosulfonate in 2 ml of dry tetrahydrofuran at 0°C under nitrogen. After stirring for 45 minutes, the resulting solution was poured into water and extracted with chloroform. The chloroform solution was dried over anhydrous $Na_2SO_4$ and evaported *in vacuo* to give an oil. This was dissolved in 1:1 chloroform-hexane and chromatographed on a 20 g-silica gel column, eluting successively with chloroform-hexane (1:1) and chloroform to give 72 mg of the title compound.

Another run on the same scale gave 80 mg more of the title compound.

C) 9-Fluoro-11β-hydroxy-17β-(methylthio)-17-(propylthio)androsta-1,4-diene-3,16-dione

A solution of 152 mg (0.316 mmole) of 11β-(acetyloxy)-9-fluoro-17β-(methylthio)-17-(propylthio)androsta-1,4-diene-3-,16-dione in a mixture of methanol (15 ml), tetrahydrofuran (10 ml) and water (1 ml) was stirred with 0.1 ml of 3M sodium hydroxide solution at room temperature under nitrogen for one hour. The resulting solution was quenched with a slight excess of acetic acid. The solvent was evaporated *in vacuo* to give a slurry. This was diluted with water and extracted with chloroform. The chloroform solution was dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* to give a foam. This was redissolved in a small amount of chloroform and chromatographed on 3 precoated silica gel TLC plates (E. Merck, 20 cm × 20 cm × 0.5 mm, 1:4 ethyl acetate-chloroform for development) to give the title compound. Crystallization from acetone-hexane gave 115 mg of an analytical specimen, melting point 246—248°C (*dec.*)

## Example 5

### (11β, 17β)-17-(Ethylthio)-9-fluoro-11-hydroxy-17-(propylthio)-androsta-1,4-diene-3,16-dione

11β-(Acetyloxy)-17,17-bis(ethylthio)-9-fluoro-16α-methyoxyandrosta-1,4-dien-3-one

A solution of 1.6 g (3.52 mmole) of 11β,16α)-17,17-bis(ethylthio)-9-fluoro-11-hydroxy-16-methyoxyandrosta-1,4-dien-3-one in 20 ml of pyridine was stirred at 110° (oil bath temperature) with 10 ml of acetic anhydride for 24 hours under nitrogen. The solvent from the resulting colored solution was evaporated *in vacuo*. The residue was diluted with water and extracted with chloroform. The chloroform solution was washed with cold 5% hydrochloric acid, water and a dilute sodium bicarbonate solution, dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give a colored gum. This was chromatographed on a 30 g silica gel column, eluting successively with chloroform-hexane (1:1) and chloroform-ethyl acetate (98:2) to give 1.7 g (97.3%) of a tlc homogeneous title compound with consistent spectral data.

11β-Acetyloxy-17β-(ethylthio)-9-(fluoro)-androsta-1,4-dien-3,16-dione

A solution of 1.6 g of (3.22 mmole) of 11β-acetyloxy-17,17-bis(ethylthio)-9-fluoro-16α-methoxyandrosta-1,4-dien-3-one in 40 ml of diethylbenzene containing 2 drops of water was heated at 190—195° (oil bath temperature) for 2.5 hours. The resulting solution was cooled to room temperature and chromatographed on a 80 g silica gel column, eluting successively with chloroform-hexane (2:3), chloroform and chloroform-ethyl acetate (95:5) to give 625 mg (46.1%) of the title compound with consistent spectral data.

11β-Acetyloxy)-17β-(ethylthio)-9-fluoro-17-(propylthio)-androsta-1,4-diene-3,16-dione

To a solution of 225.6 mg (2.23 mmole) of dry diisopropylamine in 5 ml of dry tetrahydrofuran at −78° (acetone-Dry ice bath) was added dropwise 1.33 ml of n-butyllithium (1.7M in hexane) under nitrogen. After stirring 20 minutes at −78°, a solution of 625 mg (1.486 mmole) of -11β-acetyloxy-17β-(ethylthio)-9-(fluoro)-androsta-1,4-diene-3,16-dione in 3 ml of dry tetrahydrofuran was added dropwise. The mixture was gradually warmed to 0° in the course of 2 hours. This was then slowly added into a solution of 1.5 g (9.48 mmole) of n-propyl-n-propanethiosulfonate in 5 ml of dry tetrahydrofuran at 0° under nitrogen. After stirring for 1.0 hour, the resulting solution was poured into water and extracted with chloroform. The chloroform solution was dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* at 35° to give an oil. This was redissolved in chloroform and chromatographed on a 35 g silica gel column, eluting successively with chloroform-hexane (4:1), chloroform and chloroform-ethyl acetate (95:5) to give 310 mg (42.2%) of the title compound, with consistent spectral data.

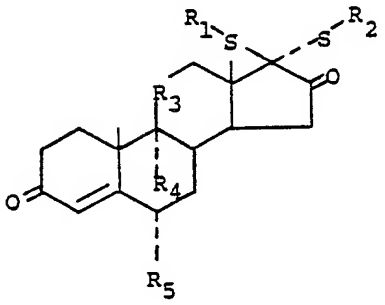
(11β, 17β)-17-(Ethylthio)-9-fluoro-11-hydroxy-17-(propylthio)-androsta-1,4-diene-3,16-dione

A solution of 310 mg (0.627 mmole) of 11β-acetyloxy-17β-(ethylthio)-9-fluoro-17-(propylthio)androsta-1,4-diene-3,16-dione in 25 ml of methanol and 1.0 ml of water was stirred with 1.0 ml of sodium hydroxide solution (3M) at room temperature under nitrogen for 1.0 hour. The resulting solution was quenched with a slight excess of glacial acetic acid. The solvent was evaporated *in vacuo* to give a slurry. This was diluted with water, extracted with chloroform, dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* to give a foam. This was redissolved in a small amount of chloroform and chromatographed on 3 precoated silica gel TLC plates (E. Merck, 20 cm × 20 cm × 0.5mm, 1:4 ethyl acetate-chloroform for development) to give a tlc-homogeneous title compound. Crystallization from acetone-hexane gave 145 mg (51.1%) of an analytical specimen, m.p. 231—233°C (dec), with consistent spectral data.

| | | | | | |
|---|---|---|---|---|---|
| Anal. Calc'd for $C_{24}H_{33}FO_3S_2$: | C, 63.68; | H, 7.35; | F, 4.20; | S, 14.17 |
| Found: | C, 63.45; | H, 7.31; | F, 4.25; | S, 14.03 |

**Claims for the Contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

1. A steroid having the formula



or 1,2-dehydro and 6,7-dehydro derivatives thereof, wherein $R_1$ and $R_2$ are the same or different and each is alkyl, cycloalkyl or aryl;

$R_3$ is carbonyl, β-hydrooxmethylene or β-acetyloxymethylene;

$R_4$ is hydrogen or halogen; and

$R_5$ is hydrogen, methyl, hydroxy, alkanoyl, alkanoyloxy, or halogen.

2. A steroid in accordance with claim 1 wherein $R_3$ is β-hydroxymethylene.

3. A steroid in accordance with claim 1 wherein $R_4$ is fluorine.

4. A steroid in accordance with claim 1 wherein $R_5$ is hydrogen.

5. A steroid in accordance with claim 1 wherein $R_3$ is β-hydroxymethylene, $R_4$ is fluorine and $R_5$ is hydrogen.

6. A steroid in accordance with claim 1 wherein $R_1$ and $R_2$ are each methyl.

7. A steroid in accordance with claim 5 wherein $R_1$ and $R_2$ are each methyl.

8. A steroid in accordance with claim 1 wherein one of $R_1$ and $R_2$ is methyl and the other is ethyl.

9. A steroid in accordance with claim 5 wherein one of $R_1$ and $R_2$ is methyl and the other is ethyl.

10. The steroid in accordance with claim 1, 9-fluoro-11β-hydroxy-17,17-bis(methylthio)-androsta-1,4-diene-3,16-dione.

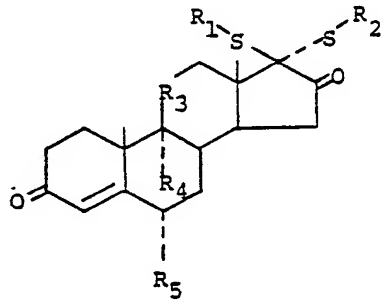
11. The steroid in accordance with claim 1, 17α-(ethylthio)-9-fluoro-11β-hydroxy-17-(methylthio)androsta-1,4-diene-3,16-dione.

12. The steroid in accordance with claim 1, 17,17-bis(ethylthio)-9-fluoro-11β-hydroxy-androsta-1,4-diene-3,16-dione.

13. The steroid in accordance with claim 1, 9-fluoro-11β-hydroxy-17β-(methylthio)-17-(propylthio)androsta-1,4-diene-3,16-dione.

**Claims for the Contracting State: AT**

1. A process for preparing compounds having the formula



I

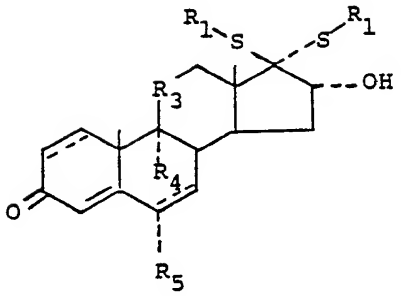
and the 1,2-deydro and 6,7-dehydro derivatives wherein $R_1$ and $R_2$ are the same and each is alkyl, cycloalkyl or aryl;

$R_3$ is carbonyl, β-hydroxymethylene or β-acetyloxymethylene;

$R_4$ is hydrogen or halogen; and

$R_5$ is hydrogen, methyl, hydroxy, alkanoyl, alknoyloxy, or halogen which comprises oxidizing a compound having the formula

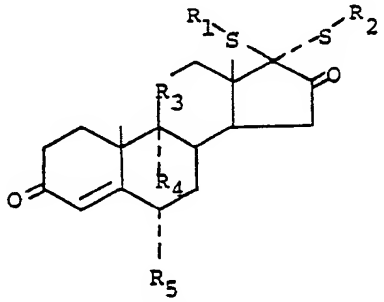
II



to yield a compound of formula I wherein $R_1$ and $R_2$ are the same.

2. A process according to Claim 1 wherein the oxidation is carried out with dimethylsulfoxide and acetic anhydride.

3. A process for preparing compounds having the formula



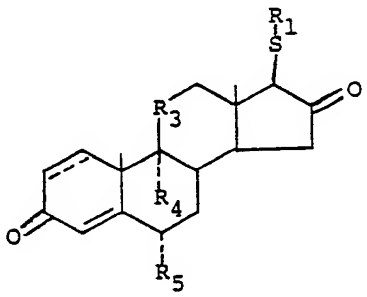
and the 1,2-dehydro and 6,7-dehydro derivatives wherein $R_1$ and $R_2$ are different and each is alkyl, cycloalkyl or aryl;

$R_3$ is carbonyl, β-hydroxymethylene or β-acetyloxymethylene;

$R_4$ is hydrogen or halogen; and

$R_5$ is hydrogen, methyl, hydroxy, alkanoyl, alkanoyloxy, or halogen which comprises reacting a compound having the formula:

V



with a compound having the formula

$$R_2\text{-}S\text{-}SO_2\text{-}R_2 \qquad \text{VI}$$

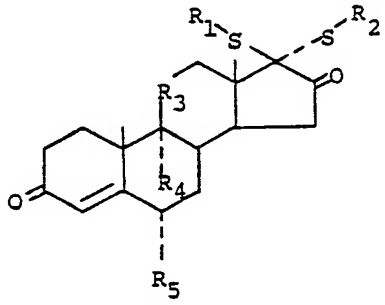
in the presence of an organic solvent, a base and a secondary amine.

4. A process according to Claim 3 wherein the reaction is carried out in the presence of tetrahydrofuran, n-butyl lithium and diisopropylamine.

5. A process according to Claim 2 and 3 wherein the 11β-hydroxyl group is protected during the reaction and then deprotected to yield compounds wherein $R_3$ is hydroxymethylene.

**Patentansprüche für die Vertragsstaaten BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

1. Steroid der Formel



oder 1,2-Dehydro- und 6,7-Dehydro-Derivate davon, wobei $R_1$ und $R_2$ gleich oder verschieden sind und jeweils einen Alkyl-, Cycloalkyl- oder Arylrest bedeuten;

$R_3$ eine Carbonyl-, β-Hydroxymethylen- oder β-Acetyloxy-methylengruppe darstellt;

$R_4$ ein Wasserstoff- oder Halogenatom ist; und

$R_5$ ein Wasserstoffatom, eine Methylgruppe, eine Hydroxylgruppe, einen Alkyanoylrest, einen Alkyanoyloxyrest oder ein Halogenatom bedeutet.

2. Steroid nach Anspruch 1, in dem $R_3$ eine β-Hydroxymethylengruppe bedeutet.

3. Steroid nach Anspruch 1, in dem $R_4$ ein Fluoratom bedeutet.

4. Steroid nach Anspruch 1, in dem $R_5$ ein Wasserstoffatom bedeutet.

5. Steroid nach Anspruch 1, in dem $R_3$ eine β-Hydroxymethylengruppe, $R_4$ ein Fluoratom und $R_5$ ein Wasserstoffatom bedeutet.

6. Steroid nach Anspruch 1, in dem $R_1$ und $R_2$ jeweils eine Methylgruppe bedeuten.

7. Steroid nach Anspruch 5, in dem $R_1$ und $R_2$ jeweils eine Methylgruppe bedeuten.

8. Steroid nach Anspruch 1, in dem einer der Reste $R_1$ und $R_2$ eine Methylgruppe und der andere eine Äthylgruppe bedeutet.

9. Steroid nach Anspruch 5, in dem einer der Reste $R_1$ und $R_2$ eine Methylgruppe und der andere eine Äthylgruppe bedeutet.

10. Steroid nach Anspruch 1, nämlich 9-Fluor-11β-hydroxy-17,17-bis(methylthio)-androsta-1,4-dien-3,16-dion.

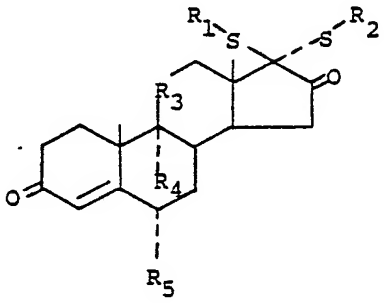
11. Steroid nach Anspruch 1, nämlich 17α-(Äthylthio)-9-fluor-11β-hydroxy-17-(methylthio)androsta-1,4-dien-3,16-dion.

12. Steroid nach Anspruch 1, nämlich 17,17-Bis(äthylthio)-9-fluor-11β-hydroxy-androsta-1,4-dien-3,16-dion.

13. Steroid nach Anspruch 1, nämlich 9-Fluor-11β-hydroxy-17β-methylthio-17(propylthio)androsta-1,4-dien-3,16-dion.

**Patentansprüche für den Vertragsstaat AT**

1. Verfahren zur Herstellung von Verbindungen der Formel:



I

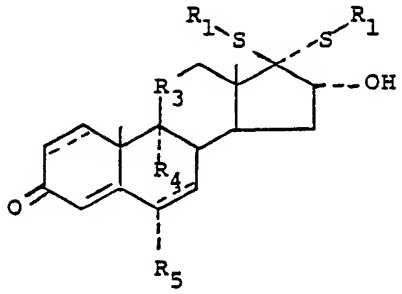
und der 1,2-Dehydro- und 6,7-Dehydro-Derivate, in denen $R_1$ und $R_2$ gleich sind und jeweils einen Alkyl-, Cycloalkyl- oder Arylrest bedeuten;

$R_3$ eine Carbonyl-, β-Hydroxymethylen- oder β-Acetyloxymethylengruppe darstellt;

$R_4$ ein Wasserstoffatom oder Halogenatom ist; und

$R_5$ ein Wasserstoffatom, eine Methylgruppe, eine Hydroxylgruppe, einen Alkanoylrest, einen

Alkanoyloxyrest oder ein Halogenatom bedeutet, gekennzeichnet durch die Oxidation einer Verbindung der Formel:

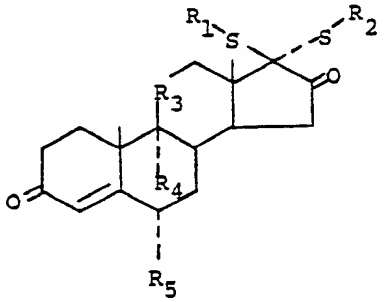


II

zu einer Verbindung der Formel I, in der $R_1$ und $R_2$ die gleiche Bedeutung haben.

2. Verfahren nach Anspruch 1, in dem die Oxidation mit Dimethylsulfoxid und Essigsäureanhydrid durchgeführt wird.

3. Verfahren zur Herstellung von Verbindungen der Formel:

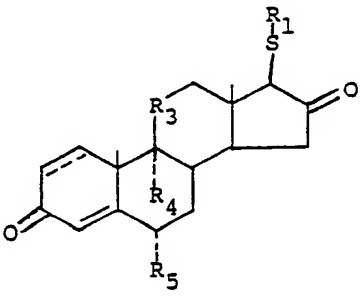


und der 1,2-Dehydro- und 6,7-Dehydro-Derivate, in denen $R_1$ und $R_2$ verschieden sind und jeweils einen Alkylrest, Cycloalkyl- oder Arylrest bedeuten;

$R_3$ einen Carbonyl-, β-Hydroxymethylen- oder β-Acetyloxymethylengruppe darstellt;

$R_4$ ein Wasserstoff-oder Halogenatom ist; und

$R_5$ ein Wassertoffatom eine Methylgruppe, eine Hydroxygruppe, einen Alkanoylrest, einen Alkanoyloxyrest oder ein Halogenatom bedeutet, gekennzeichnet durch die Umsetzung einer Verbindung der Formel



V

mit einer Verbindung der Formel

$$R_2\text{-}S\text{-}SO_2\text{-}R_2 \qquad \text{VI}$$

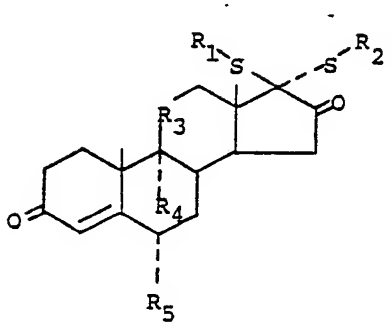
in Gegenwart eines organischen Lösungsmittels, einer Base und eines sekundären Amins.

4. Verfahren nach Anspruch 3, in dem die Umsetzung in Gegenwart von Tetrahydrofuran, n-Butyllithium und Diisopropylamin durchgeführt wird.

5. Verfahren nach den Ansprüchen 2 und 3, in dem die 11β-Hydroxylgruppe während der Umsetzung geschützt ist und anschließend die Schutzgruppe entfernt wird, wobei man Verbindungen erhält, in denen $R_3$ eine Hydroxymethylengruppe ist.

**Revendications pour les Etats contractants: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

1. Stéroïde de formule



ainsi que ses dérivés 1,2-déhydrogénés et 6,7-déhydrogénés, formule dans laquelle $R_1$ et $R_2$ sont identiques ou différents et sont chacun un radical alkyle, cycloalkyle ou aryle;

$R_3$ est un groupement carbonyle, β-hydroxyméthylène ou β-acétyloxyméthylène;

$R_4$ est un atome d'hydrogène ou d'halogène; et

$R_5$ est un atome d'hydrogène, un radical méthyle, un groupement hydroxy, un radical alcanoyle ou alcanoyloxy, ou un atome d'halogène.

2. Stéroïde selon la revendication 1, dans la formule duquel $R_3$ est un groupement β-hydroxyméthylène.

3. Stéroïde selon la revendication 1, dans la formule duquel $R_4$ est un atome de fluor.

4. Stéroïde selon la revendication 1, dans la formule duquel $R_5$ est un atome d'hydrogène.

5. Stéroïde selon la revendication 1, dans la formule duquel $R_2$ est un groupement β-hydroxyméthylene, $R_4$ est un atome de fluor et $R_5$ est un atome d'hydrogène.

6. Stéroïde selon la revendication 1, dans la formule duquel $R_1$ et $R_2$ sont chacun un radical méthyle.

7. Stéroïde selon la revendication 5, dans la formule duquel $R_1$ et $R_2$ sont chacun un radical méthyle.

8. Stéroïde selon la revendication 1, dans la formule duquel l'un des substituants $R_1$ et $R_2$ est un radical méthyle et l'autre est un radical éthyle.

9. Stéroïde selon la revendication 5, dans la formule duquel l'un des substituants $R_1$ et $R_2$ est un radical méthyle et l'autre est un radical éthyle.

10. Stéroïde selon la revendication 1, qui est la 9-fluoro-11β-hydroxy-17,17-bis(méthylthio)androsta-1,4-diène-3,16-dione

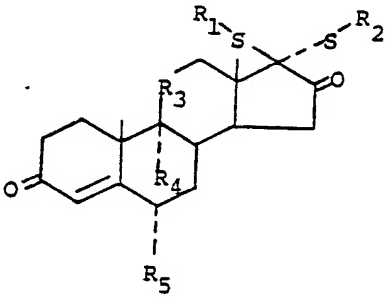
11. Stéroïde selon la revendication 1, qui est la 17α-(éthylthio)-9-fluoro-11β-hydroxy-17-(méthylthio)-androsta-1,4-diène-3,16-dione.

12. Stéroïde selon la revendication 1, qui est la 17,17-bis(éthylthio)-9-fluoro-11β-hydroxyandrosta-1,4-diène-3,16-dione.

13. Stéroïde selon la revendication 1, qui est la 9-fluoro-11β-hydroxy-17β-(méthylthio)-17-(propylthio)-androsta-1,4-diène-3,16-dione.

**Revendications pour l'Etat contractant: AT**

1. Procédé de préparation de composés ayant pour formule:



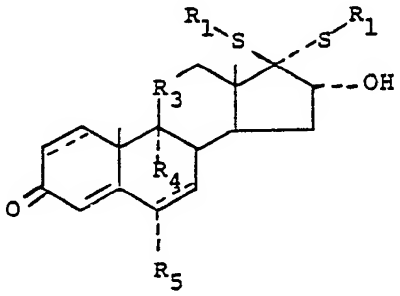
I

et de leurs dérivés 1,2-déhydrogénés et 6,7-déhydrogénés, formule dans laquelle $R_1$ et $R_2$ sont identiques et sont chacun un radical alkyle , cycloalkyle or aryle;

$R_3$ est un groupement carbonyle, β-hydrométhyléne ou β-acétyloxyméthylène;

$R_4$ est un atome d'hydrogène ou d'halogène; et

$R_5$ est un atome d'hydrogène un radical méthyle, un groupment hydroxy, un radical alcanoyle ou alcanoyloxy, ou un atome d'halogène qui consiste à oxyder un composè ayant pour formule

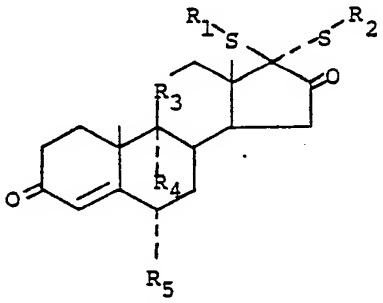


II

pour obtenir un composé de formule I dans laquelle $R_1$ et $R_2$ sont identiques.

2. Procédé selon la revendication 1, dans lequel on réalise l'oxydation avec du diméthylsulfoxyde et de l'anhydride acétique.

3. Procédé de préparation de composés ayant pour formule

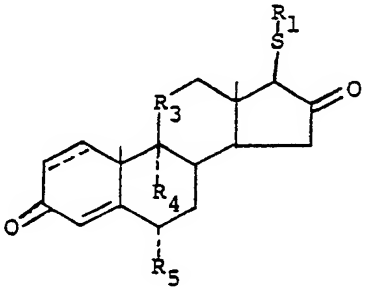


et de leurs dérivés 1,2-déhydrogénés et 6,7-déhydrogénés, formule dans laquelle $R_1$ et $R_2$ sont différents et sont chacun un radical alkyle, cycloalkyle ou alkyle;

$R_3$ est un groupment carbonyle, β-hydroxyméthylène ou β-acétyloxyméthylène;

$R_4$ est un atome d'hydrogène ou d'halogène; et

$R_5$ est un atome d'hydrogène, un radical méthyle, un groupment hydroxy, un radical alcanoyle ou alcanoyloxy, ou un atome d'halogène qui consiste à faire réagir un composé ayant pour formule:



V

avec un composé ayant pour formule

$$R_2\text{-}S\text{-}SO_2\text{-}R_2$$

VI

en présence d'un solvant organique, d'une base et d'une amine secondaire.

4. Procédé selon la revendication 3, dans lequel on méne la réaction en présence de tétrahydrofuranne, de n-butyl lithium et de diisopropylamine.

5. Procédé selon les revendications 2 et 3, dans lequel on protège le groupement 11β-hydroxyle pendant la réaction, puis on supprime sa protection pour obtenir les composés dans la formule desquels $R_3$ est un groupment hydroxyméthylène.